CLAIMS

We claim:

1. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a ubiquitin-specific protease gene;

(b) a second polynucleotide sequence homologous to the ubiquitin-specific protease gene; and

(c) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a ubiquitin-specific protease gene;

(b) providing a second polynucleotide sequence homologous to the ubiquitin-specific protease;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

4. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a ubiquitin-specific protease gene and a second sequence homologous to a second region of a ubiquitin-specific protease gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

5. A cell comprising a disruption in a ubiquitin-specific protease gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in a ubiquitin-specific protease gene.

9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a ubiquitin-specific protease gene, the method comprising:

(a) introducing the targeting construct of claim 1 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

11. A method of identifying an agent that modulates the expression of a ubiquitin-specific protease, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a ubiquitin-specific protease gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of a ubiquitin-specific protease in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the function of a ubiquitin-specific protease, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a ubiquitin-specific protease gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted ubiquitin-specific protease gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of a ubiquitin-specific protease, the method comprising:

(a) providing a cell comprising a disruption in a ubiquitin-specific protease gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the ubiquitin-specific protease is modulated.

14. A method of identifying an agent that modulates the function of a ubiquitin-specific protease gene, the method comprising:

(a) providing a cell comprising a disruption in a ubiquitin-specific protease gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the ubiquitin-specific protease gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in a ubiquitin-specific protease gene, wherein the transgenic mouse exhibits increased PPI.

18. A method of producing a transgenic mouse comprising a disruption in a ubiquitin-specific protease gene, wherein the transgenic mouse exhibits increased PPI, the method comprising:

(a) introducing a ubiquitin-specific protease gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a ubiquitin-specific protease.

19. A cell derived from the transgenic mouse of claim 17 or claim 18.

20. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a ubiquitin-specific protease gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a ubiquitin-specific protease gene; and

(b) determining whether the agent ameliorates increased PPI.

21. A method of identifying an agent which modulates ubiquitin-specific protease gene expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a ubiquitin-specific protease gene; and

(b) determining whether the agent modulates ubiquitin-specific protease expression in the transgenic mouse, wherein the agent has an effect on increased PPI.

22. A method of identifying an agent which modulates ubiquitin-specific protease gene function, the method comprising:

(a) providing a cell comprising a disruption in a ubiquitin-specific protease gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates ubiquitin-specific protease gene function, wherein the agent modulates a phenotype associated with a disruption in a ubiquitin-specific protease gene.

23. The method of claim 22, wherein the phenotype comprises increased PPI.

24. An agent identified by the method of claim 20, claim 21, or claim 22.

25. An agent that modulates the function, expression or activity of a ubiquitin-specific protease gene.